THE SUPERFICIAL GLANDS OF THE ŒSOPHAGUS.

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PLATE XXI.

The glands of the œsophagus are of two varieties. Of these the submucous glands have long been recognized. F. A. Schmidt[1] in 1805 described them and there have been many descriptions since then. They are typical mucous glands situated in the submucous coat of the œsophagus (Plate XXI, Fig. 2). Their ducts pierce the muscularis and frequently show cystic dilatations before emptying by their comparatively narrow mouths. The ducts are lined for some distance from their orifices by a stratified epithelium of cuboidal cells. They frequently pass through lymphatic nodules or lie close to them. The secreting cells and the contents of the ducts stain deeply with stains for mucin.

The other variety of glands is totally distinct from these submucous glands, and as they are best characterized by their situation superficial to the muscularis mucosæ, I shall speak of them as the superficial glands of the œsophagus (glandulæ œsophageæ superficiales). They occur mainly in two localities in the œsophagus: (1) in areas in its upper portion, and (2) at the transition of stomach and œsophagus. These latter, the so-called "Cardiadrüsen," extend but a short way toward the stomach, being soon replaced by the typical fundus glands. Toward the œsophagus they may extend a short distance beneath the stratified epithelium or occur in little groups just above the gastro-œsophageal junction. They have been grouped by some with the gastric glands. The areas of superficial glands which

[1] De mammalium œsophago atque ventriculo. Inaug.-Diss., Halle, 1805.

are found in the upper œsophagus will be considered especially in this paper.[2]

Rüdinger[3] described these glands in 1879 as tubulo-acinous glands of the œsophagus lying above the muscularis mucosæ. According to his description they are situated in the lateral wall of the upper part of the œsophagus but are not bilateral. He describes them as consisting of three portions: (1) narrow peripheral tubules lined by pyramidal cells; (2) large cavities into which the tubules empty; (3) the ducts to these cavities which lead to the surface. The cavities and ducts are lined by high cylindrical cells. W. Krause[4] probably had Rüdinger's work in mind when, in 1879, he classified the œsophageal glands as (1) the common, isolated glands in the submucosa, (2) the smaller glands in the mucous membrane of the lower œsophagus, and (3) a tubular variety of glands at the upper end of the œsophagus. In 1887, Lauteschläger,[5] after examination of several œsophagi, was unable to confirm Rüdinger's observations.

With these exceptions, Rüdinger's work had passed unnoticed and these glands had been overlooked or misinterpreted, until J. Schaffer,[6] in 1897, again called attention to them. He had his attention directed to an area $6\frac{1}{2}$ mm. by 4 mm. in the œsophagus of a girl eleven years of age. This proved to be made up of glands superficial to the muscularis mucosæ. He found similar though smaller areas in other œsophagi, but he was unable to find the glands in one œsophagus, from the upper part of which serial sections were made of a piece $1\frac{1}{2}$ centimetres long. He found the glands to be bilateral and located between the levels of the cricoid and the fifth tracheal cartilage. He describes the glands as consisting of a number of twisted and branched tubules of varying diameters

[2] Schaffer calls these glands "die obere Cardiadrüsen," but as the glands in the fundus of the stomach have been designated by some English writers as "the cardiac glands," I have, in order to avoid the suggestion of identifying these œsophageal glands in structure with the latter, preferred the term "superficial glands of the œsophagus" to Schaffer's designation.

[3] Beiträge zur Morphologie des Gaumensegels und des Verdauunsgsapparates, pp. 27–31. Stuttgart, 1879.

[4] Handbuch der menschlichen Anatomie, ii, p. 445. Hannover, 1879.

[5] Beiträge zur Kenntniss der Halseingeweide des Menschen. Inaug.-Diss., Würzburg, 1887.

[6] Ueber die Drüsen der menschlichen Speiseröhre. *Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl.*, Wien, 1897, cvi, p. 175. Beiträge zur Histologie menschlicher Organe. Ibid., cvi, p. 403. Epithel und Drüsen der Speiseröhre. *Wien. klin. Wochenschr.*, 1898, xi, p. 533.

lined by low cylindrical or cuboidal cells. Among these cylindrical cells he found parietal cells in varying numbers in each of his specimens. These tubules empty either directly or by means of wide spaces into the duct. The duct may be dilated, but its opening is always narrow and it always comes to the surface at the top of a papilla. When several such ducts have a common place of emptying, the stratified epithelium is pushed aside and the area is covered by columnar epithelium. Schaffer showed that these glands are morphologically identical with the glands found at the transition of the œsophagus and stomach (Cardiadrüsen).

On the same date that Schaffer presented his first article, Eberth [7] described an area in the œsophagus which he interpreted as misplaced gastric epithelium. It presented a round, reddish and well circumscribed surface about the size of a five-Pfennig piece at about the middle of the œsophagus. On microscopic examination it was seen that the stratified epithelium ceased abruptly, being replaced by a great number of tubular "mucous" glands analogous to those in the stomach. Eberth did not find similar areas in other œsophagi. Although this area was at a lower level than is common for the superficial glands there seems no doubt but that it was such a glandular area.

Oppel,[8] in a review of Schaffer's work, speaks of the interesting comparison between the superficial glands of the upper œsophagus and the glands at the transition of the œsophagus and stomach. He deems it important to have a confirmation of Schaffer's work, and especially of the occurrence of parietal cells in the œsophagus. Hildebrand [9] in 1898 reported a single case of the "occurrence of gastric glands in the œsophagus," which he regards as identical with those described by Schaffer and by Eberth. In his case there were paired areas of glands in the upper œsophagus and these contained parietal cells. In the last edition of Quain's Anatomy [10] it is stated that a few of the smallest of the œsophageal glands are situated in the substance of the mucous membrane. Such are undoubtedly superficial glands. Böhm and v. Davidoff [11] describe the œsophageal glands as emptying at the apices of the papillæ, which is true only for the superficial glands and not for the

[7] Verirrtes Magen-Epithel in der Speiseröhre. *Fortschr. d. Med.*, 1897, xv, p. 261.

[8] Lehrb. d. vergleichenden microscopischen Anatomie d. Wirbelthiere, ii, p. 153. Jena, 1897.

[9] Ueber das Vorkommen von Magendrüsen im Oesophagus. *Münch. med. Wochenschr.*, 1898, xlv, p. 1057.

[10] Quain's Anatomy, edited by E. A. Schäfer and G. D. Thane, Vol. iii, Pt. iv, p. 66 London, 1896.

[11] Lehrbuch der Histologie des Menschen, pp. 170–171, Wiesbaden, 1895.

more common submucous glands. Their representation of an œsophageal gland [12] also appears to me to be a superficial gland and not a submucous gland.

In 1899, without previous knowledge of Rüdinger's or Schaffer's publications, the attention of Dr. Ophüls, Professor of Pathology and Bacteriology at Cooper Medical College, San Francisco, was called to these superficial œsophageal glands, by finding two corresponding "oval defects" in the mucous membrane of the œsophagus of a patient who died of pneumonia. These defects were upon its lateral walls, were symmetrical, and were opposite the upper tracheal cartilages, 5½ cm. below the opening of the larynx (Plate XXI, Fig. 1). The long axis of each, measuring 2 cm., was parallel to the long axis of the œsophagus; the width of each was 0.5 cm. The surface was somewhat lower than that of the surrounding mucous membrane and was smooth, glistening and dark red in color, so that these areas looked not unlike ulcers, although on account of their symmetry and regularity of outline this idea was dismissed and a congenital misplacement was suspected. Sections showed these areas to consist of tubular glands superficial to the muscularis mucosæ.

In ten consecutive autopsies, similar but smaller glandular areas were recognized in five cases macroscopically, and these findings were confirmed in each instance by microscopic examination. The size of the areas in these five cases varied from 3 mm. to 8 mm. in the longest diameter. They were circular or more or less oval, and when oval the long axis was parallel to the long axis of the œsophagus. The location in each case fell within the limits as given by Schaffer, namely, on the lateral wall of the œsophagus from the level of the cricoid to that of the fifth tracheal cartilage. They were noted to be bilateral in two cases. One specimen which was at first supposed to contain only a single area was demonstrated upon microscopic examination to present a corresponding smaller area on the other side. This shows how easily a few of these glands may be overlooked. The size of an area therefore may vary greatly: from one invisible to the

[12] Op. cit., Fig. 121.

unaided eye to such a large area as that in our first specimen. There may be only a few glands present, separated from one another by areas of connective tissue and smooth muscle, their ducts opening at separate places through the squamous epithelium. In such cases the squamous epithelium over the glands is of diminished thickness and the papillæ are either small or absent. Such an area appears in the gross as a small nodular bulging in the mucous membrane, usually somewhat larger than the elevations produced by the submucous glands. In other cases, the glands may be so closely packed as to simulate the gastric glands in appearance, although strands of connective tissue are still seen dividing the tubules into groups. In such

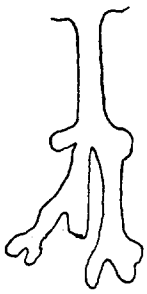

FIG. A.—Diagram of a simple form of superficial gland. Drawn from a reconstruction. x 70.

a case, the stratified squamous epithelium ends abruptly at the glandular areas, the Malpighian layer bending at almost a right angle and becoming continuous with the single layer of columnar cells covering the irregular surface between the mouths of the ducts (Plate XXI, Fig. 2). Such an area looks to the naked eye not unlike an ulcer with well defined edges. It presents a low, red, glistening surface that readily attracts notice on careful examination of the œsophagus.

The glands are of the branched tubular type. They are remarkable for their many windings as well as for their cyst-like spaces. It is rare to see a gland cut longitudinally for any distance on account of the irregular course which it pursues. The complexity of the glands and the number of branches varies greatly. Fig. A drawn from a reconstruction is a schematic representation of one of the simplest

of these glands if its branches were laid in one plane. It is seen to consist of a duct and several acini. The duct (Fig. B, d) is lined by

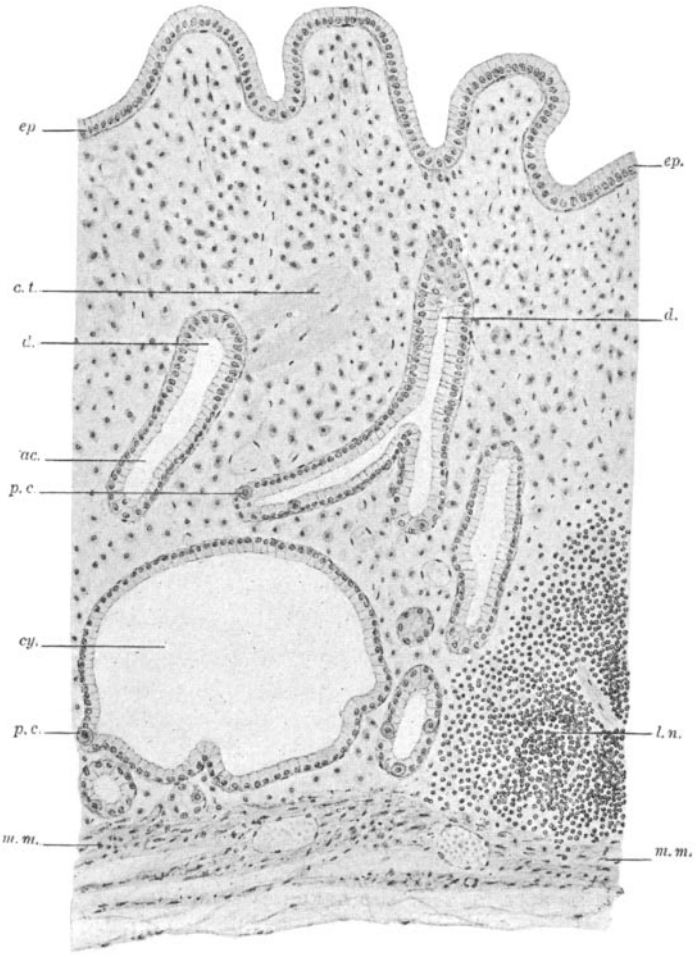

FIG. B.—Drawing of a section of the superficial gland area, x 130. *ep.* columnar epithelium of the surface, *d.* duct, *ac.* acinus, *cy.* cystic dilatation of an acinus, *p. c.* parietal cells, *c. t.* strands of dense connective tissue, *m. m.* muscularis mucosæ, *l. n.* lymphatic nodule.

high columnar cells two to four times as high as they are broad. The nuclei are oval with their long axes parallel to the long axes of the cells. They are situated all at about the same level, a short distance

from the base of the cell. A few ducts contain what appear to be goblet cells among the other cells. Where the gland begins to branch, the character of the epithelium changes. The cells become shorter and more conical. The nuclei become spherical or oval with the axis at right angles to the axis of the cell or even flattened transversely against the base of the cell. Their situation is uniformly nearer the base of the cell than is that of the nuclei of the duct cells (Fig. B, *ac.*, and Plate XXI, Fig. 3). The protoplasm of these acinous cells appears reticulated.

In the acini of many of the glands cells of another type are seen, identical with the parietal cells of the gastric tubules. These are round or oval cells which are usually readily distinguished on account of their property of staining deeply with eosin and picric acid. The nucleus is located at about the centre of the cell (Fig. B, *p. c.*, and Plate XXI, Fig. 3). These cells frequently possess two or three nuclei and occasionally a cell may have four or five. The cell body appears almost homogeneous in some specimens, but in others it is seen to be filled with small refractive granules densely packed together. Clear spaces in the protoplasm, apparently vacuoles, are of frequent occurrence in these cells. It will be seen that in all these particulars they agree in structure with the parietal cells of the stomach. Schaffer states that he found parietal cells in each of his first six specimens. I was not able to find them with such regularity and succeeded in demonstrating these cells in only three of six specimens. They certainly vary greatly in number in the different œsophagi, for in two cases they were present only in small numbers, while in our original specimen they were the prevailing cells in many tubules.

One of the distinguishing features of these glands is the presence of cystic cavities (Fig. B, *cy*). These were present in some of the glands of each specimen examined, but they showed great irregularity in size and shape. Their diameters varied up to 0.7 mm. The epithelium lining these cystic structures is usually like that lining the ducts of the glands. Other cysts, however, and especially those situated deeply in the mucosa, are lined by low columnar cells of the type found in the gland tubules, and, in addition, they may contain parietal cells (Fig. B, *cy.*; *p. c.*). Still other cysts have duct epithelium lining

their superficial portions and glandular epithelium lining their deeper portions. It would appear, therefore, that these cystic structures may be due to dilatations of different parts of the gland. That they are not present in every gland, as Rüdinger thought, is shown by their absence in the gland represented in Fig. A. The portion of the gland which is more commonly dilated is the duct and less frequently it is the secreting tubule, and this accounts for the variability in the cell-lining of the cysts. These dilatations are, as a rule, least frequent in the glands which are richest in parietal cells, and most frequent in glands containing no parietal cells. They are filled usually with a mucoid material containing desquamated cells and cellular debris. These cystic structures are comparable to the dilatations which occur in the ducts of the submucous glands. The function of the latter dilatations has been regarded as that of reservoirs which hold the secretion. As the food passes down the œsophagus the mucus is pressed out and so serves to lubricate the œsophagus at a time when it is most needed. The majority of the cystic structures in the superficial glands probably act in a similar manner. Others of these, however, can hardly serve this function. A careful study of serial sections shows that in many cases, especially in the deep-seated cysts, no demonstrable communication exists between the cystic cavity and the surface. Such are, in fact, small retention cysts. The spherical shape of the larger cysts also indicates that the contents are under some considerable tension. In one place a ruptured cyst was seen with extrusion of its contents.

As Rüdinger was the first to point out, the superficial glands lie above the muscularis mucosæ, therein differing essentially from the submucous glands of the œsophagus. The muscularis mucosæ, as it approaches the gland area, usually becomes diffuse and increases in thickness. Beneath the glands it forms a thin compact layer closely applied to their bases (Fig. B, *m. m.*, and Plate XXI, Fig. 2). Where the glands are some distance apart the muscularis mucosæ may accompany the connective tissue which runs in between them. In such a case the base of the gland is surrounded by muscular fibres and when these contract they probably compress the glands and so aid in expelling their contents.

Schaffer regards the absence of a marked mucin-staining reaction in the superficial glands as an important feature distinguishing them from the submucous glands. There is a mucoid material present in the ducts and cysts, but this does not give a decided mucin-staining reaction. However, in a small number of cells sufficient mucin is present to give a very definite reaction for mucin. These cells are mostly in the lower part of the glands and in my specimens were grouped in two or three little areas, so that probably only a few of the glands contained mucin-producing cells in their acini. Whether these glands are essentially different from those in which the cells gave no mucin-staining reaction was not determined. The mucin is situated in that portion of the cell which is toward the lumen of the gland. Certain cells in the ducts of the glands also take a slight mucin stain. Yet the mucin reaction of the superficial glands as a whole is very slight compared to that of the mucous glands of the submucosa. Even in hæmatoxylin specimens, not too much decolorized, the difference is plainly seen, the submucous glands being of a deep blue color. This is well shown in Plate XXI, Fig. 2.

Lymphatic nodules are present in considerable number in the superficial gland areas. They are located just above the muscularis mucosæ corresponding to their situation in the stomach and intestine (Fig. B, *l. n.*, and Plate XXI, Fig. 2).

The morphological significance of the superficial glands is not clear. Their most interesting feature is the possession of parietal cells, which have been regarded hitherto as the special property of gastric glands. It is not strange that when many parietal cells are present, the glands containing them should be mistaken for a misplacement of gastric glands. As an explanation of their origin in his specimen, Eberth suggests that the squamous epithelium in its growth downward from above circumscribed an island of columnar epithelium which in the growth of the œsophagus became widely separated from its fellow columnar epithelium in the stomach, but like it developed into characteristic gastric glandular tissue. E. Neumann [13] showed that there

[13] Die Metaplasie des fötalen Oesophagusepithel. *Fortschr. d. Med.*, 1897, xv, p. 366.

is not a migration of stratified epithelium from above downward but that it develops in situ. Schaffer points out that both the stomach and the œsophagus are derived from the foregut and that while in the œsophagus squamous epithelium is developed, in the stomach the epithelium remains columnar and develops the gastric glands. He considers that a portion of the œsophageal mucous membrane, in failing to change to squamous epithelium, may develop similarly to the gastric mucous membrane and so give rise to gastric glands. In support of his hypothesis Schaffer has described paired areas of simple columnar epithelium in the upper œsophagus of a three-months fœtus. He regards these as an early stage in the development of the superficial glands. Why should this lack of development occur with such frequency in the upper rather than in other portions of the œsophagus? It is well known that the developmental changes in the upper œsophagus are of a more complex nature than in other regions and that this complexity seems in general to favor deviations in development. This may in part account for the gland areas in this region and also for their considerable individual variations.

Schaffer has compared the superficial glands to the œsophageal glands of some of the lower animals. Yet, if we regard the presence of parietal cells as an important feature in these glands, they have no homologue in any described structure in lower animals. The œsophageal glands of birds are above the muscularis mucosæ and in this respect they resemble the superficial glands of man. On the other hand, they are definite mucous glands and show no tendency to occur in such definite paired areas as do the superficial œsophageal glands.

The pathological relations of these glands are of interest mainly on account of their possibilities. It has been suggested that being a place of lessened resistance in the œsophageal wall a large area might gradually give way and so become the starting point for a pulsion diverticulum. The chief support for this interesting speculation comes from the fact that both the pulsion diverticula and the superficial gland areas are situated in the same region of the œsophagus. That the strength of the mucous membrane of the œsophagus is a

very important factor in the resistance to dilatation does not seem probable a priori. Should a large gland area be the point of origin of the diverticulum one would expect to find columnar epithelium in the walls of the diverticulum corresponding to the original area of superficial glands. Of special interest in this regard is König's [14] observation that two of his diverticula contained both cylindrical and flat epithelium. This seems to be the only observation of this kind on record. In a case recently in Dr. Halsted's service in the Johns Hopkins Hospital the wall of the diverticulum was lined uniformly by a pale mucous membrane which proved on section to be covered by stratified epithelium. There was no evidence of the presence of a superficial gland area.

That the glands may be a source of origin for œsophageal cysts seems probable from the fact that they commonly contain numbers of small retention cysts. The largest one in my specimens (0.7 mm.) is just visible to the unaided eye. Ordinarily these small cysts probably cease to grow larger or if they do so they are especially liable to rupture. In a few cases, however, they doubtless continue to enlarge and so give rise to one form of cysts in the œsophageal wall.

The most interesting and important question deals with the possibility of the superficial glands giving rise to carcinomata. Schaffer and Hildebrand both emphasize this possibility. I have collected from the records six cases of adeno-carcinoma of the œsophagus where the locations are mentioned, in order to see if these locations bore any relation to the location of the superficial glands. Of these carcinomata, two [15] were situated somewhat above the middle of the œsophagus, two [16] were somewhat below the middle, and two [17] more

[14] Die Extirpation des Oesophagusdivertikel. *Berl. klin. Wochenschr.*, 1894, xxxi, p. 948.

[15] F. Colle, Beiträge zur Lehre vom primären Oesophaguscarcinom. Inaug.-Diss. Göttingen, 1887.

O. Fischer, Ueber einen Fall von primärem Carcinoma myxomatodes des Oesophagus. *Prager med. Wochenschr.*, 1899, p. 391.

[16] Parmentier, *Arch. gén. de méd.*, 1889, i, p. 470.

Karewsky, Carcinom des Oesophagus. *Deutsche med. Wochenschr.*, 1892, p. 1070.

[17] D. Newman, Malignant Disease of the Throat and Nose. Edinburgh and London, 1892; cited from Rolleston in Clifford Allbutt's System of Medicine, iv, p. 374, New York, 1897.

C. P. White, *Trans. Path. Soc., London*, 1898, xlix, p. 93.

were immediately above the cardiac orifice, yet distinctly separated from the stomach. It will be seen that none of these adenocarcinomata lies within the usual limits for the superficial glands in the upper œsophagus, although the last two lie in the region of the lower superficial glands (Cardiadrüsen). The first four lie in a region where superficial glands are comparatively rare.

That the superficial glands are totally distinct from the submucous glands is easily seen where they are so well developed as in our first specimen. When they are less numerous, however, and are covered by stratified epithelium, recognition is not so easy. The most constant and important differential point is, as we have said, the relation to the muscularis mucosæ, probably all glands completely above this being superficial glands. The superficial glands tend to occur in groups in definite regions of the œsophagus. The mucous glands are generally distributed over the whole œsophagus and lie in the submucosa. The ducts of the submucous glands are lined by stratified cuboidal epithelium; the ducts of the superficial glands by a single layer of columnar cells. Lymph nodules lie about the ducts of the submucous but are beneath the bases of the superficial glands. The superficial glands frequently contain parietal cells, while the submucous glands never do. The mucous glands take a deep mucin stain; the superficial glands take it but slightly. These characteristics show that the superficial œsophageal glands are quite distinct from the submucous glands and, as a rule, are readily recognizable.

In conclusion I desire to thank Dr. Ophüls for his kind permission to report this interesting case of well developed superficial œsophageal glands, as well as for his assistance and the many favors he has shown me during my work in his laboratory.

DESCRIPTION OF PLATE XXI.

Fig. 1.—Photograph of gross specimen which had been preserved in Kaiserling's fluid. The œsophagus is opened along its left side and is turned over to the right. One of the two superficial gland areas is seen as a dark diamond-shaped area on the surface of the œsophagus. The corresponding area of the left side was removed for histological examination.

Fig. 2.—Photomicrograph of a section passing through the edge of the left superficial gland area. Hæmatoxylin and eosin stain. x 17. Above and to the

FIG. 1.

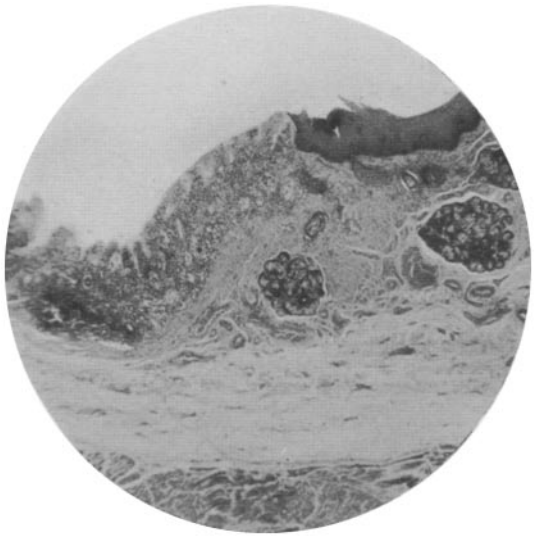

FIG. 2.

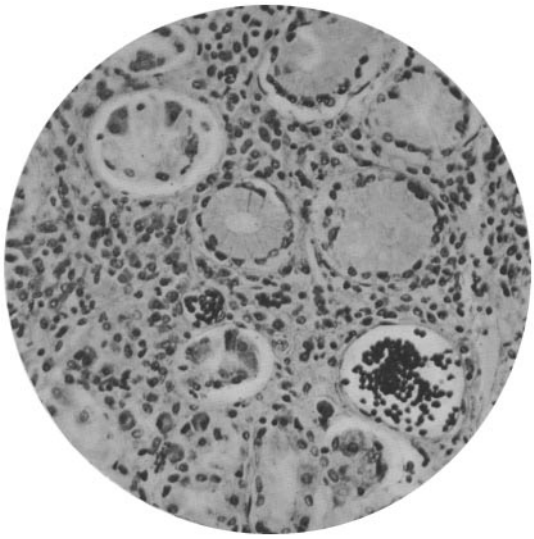

FIG. 3.

right the squamous epithelium is seen, passing toward the left, where it gives place abruptly to the superficial glands. The darkly stained, irregular ovoid masses below the muscularis mucosæ are the submucous glands with the mucus stained by the hæmatoxylin. Their ducts can be seen above them. The muscularis mucosæ is seen superficial to the submucous glands on the right. At the border of the superficial glands it is much thickened. To the left it is very thin and applied closely to the bases of the superficial glands. A lymph nodule is seen on the left just above the muscularis mucosæ. Striated muscle of the upper œsophagus is seen below.

Fig. 3.—Photomicrograph of a section near the bases of the superficial glands, x 220. Stained with Heidenhain's iron hæmatoxylin. Red blood corpuscles are deep black. Near the centre are several acini containing no parietal cells. Acini in the upper left and the lower parts of the figure contain many parietal cells.